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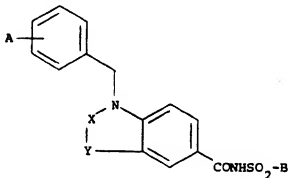
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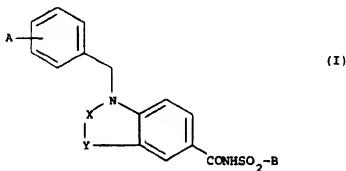
(64) **Pharmaceutical compounds.**

(57) A pharmaceutical compound of the formula



in which A is selected from -NHCOR^1 , -NHCOOR^1 , -NHCONHR^1 , -NHCSNHR^1 , -CONHR^1 , where R^1 is optionally halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-7} cycloalkyl- C_{1-4} alkyl or phenyl- C_{1-4} alkyl B is optionally substituted phenyl, and -X-Y- is -CH=CH- or $\text{-CH}_2\text{-CH}_2\text{-}$; and salts thereof. The compounds are leukotriene antagonists.

The invention relates to pharmaceutical compounds, their use and preparation.
The compounds of the invention are of the formula



in which A is selected from $-\text{NHCOR}^1$, $-\text{NHCOOR}^1$, $-\text{NHCONHR}^1$, $-\text{NHCSNHR}^1$, $-\text{CONHR}^1$, where R^1 is optionally halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-7} cycloalkyl- C_{1-4} alkyl or phenyl- C_{1-4} alkyl, B is optionally substituted phenyl, and $-\text{X}-\text{Y}-$ is $-\text{CH}=\text{CH}-$ or $-\text{CH}_2\text{CH}_2-$; and salts thereof.

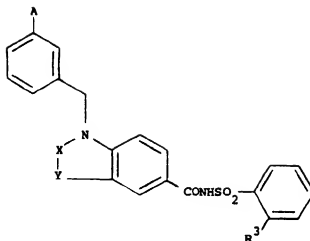
The compounds of the invention and their pharmaceutically-acceptable salts are leukotriene antagonists and are indicated for use in the treatment of diseases in which leukotrienes are a causal mediator.

In the above formula, R^1 can be optionally halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-7} cycloalkyl- C_{1-4} alkyl or phenyl- C_{1-4} alkyl. A C_{1-10} alkyl or C_{2-10} alkenyl group may be branched or unbranched and is preferably C_{1-6} alkyl or C_{2-6} alkenyl. Examples of the former include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec. butyl and tert. butyl, and preferred examples of the latter are vinyl, allyl, propenyl, 2-methyl-2-propenyl and 2-methyl-3-butenyl. When the C_{1-10} alkyl group is halo-substituted it can be substituted by one or more, such as for example 1 to 5, and especially three, halogen atoms, in particular, chloro, bromo and fluoro. Preferably the alkyl group comprises a trifluoromethyl group for instance in the terminal position. A C_{3-7} cycloalkyl- C_{1-4} alkyl group can be branched in the alkyl attachment, and is preferably of the form C_{3-7} cycloalkyl- $(\text{CH}_2)_n-$ where n is 1 to 4 and preferably 1. The cycloalkyl group can for example be cyclopropyl, cyclobutyl or cyclopentyl. A phenyl- C_{1-4} alkyl group may be branched or unbranched in the alkyl attachment, and preferably is of the form phenyl- $(\text{CH}_2)_n-$ where n is 1 to 4, a preferred instance being benzyl. R^1 is most preferably benzyl, C_{1-4} alkyl or halo-substituted C_{1-4} alkyl.

The group B is optionally substituted phenyl, and this is preferably phenyl or phenyl substituted with one or more, preferably one to three, substituents selected from C_{1-4} alkyl, especially methyl, nitro, cyano, carboxyl, amino, hydroxyl, trifluoromethyl, C_{1-4} alkoxy, especially methoxy and ethoxy, and halogen especially fluorine, chlorine or bromine. Preferably B is a phenyl ring substituted with a single substituent selected from C_{1-4} alkyl, C_{1-4} alkoxy and halogen, and especially at the ortho position.

The preferred values of A are $-\text{NHCOR}^1$, $-\text{NHCOOR}^1$, $-\text{NHCSNHR}^1$ and $-\text{NHCONHR}^1$, and the group is preferably at the meta position.

Thus a particular group of compounds according to the invention is of the formula

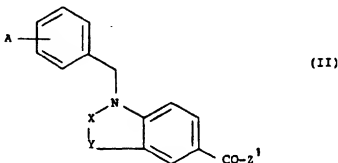


in which A is -NHCOR^1 , -NHCOOR^1 , -NHCSNR^1 or -NHCONHR^1 , -X-Y- is -CH=CH- or $\text{-CH}_2\text{-CH}_2\text{-}$, and R^3 is C_{1-4} alkyl, C_{1-4} alkoxy or halogen.

As mentioned above, the compounds of the invention when basic or acidic in free form, can exist as salts. Non-toxic addition salts are included such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycolic, maleic, hydroxymaleic, fumaric, malic, tartaric, citric, salicylic, o-acetoxybenzoic, or organic sulphonic acids for example methane sulphonc, ethane sulphonc, 2-hydroxyethane sulphonc, toluene-p-sulphonic, or naphthalene-2-sulphonic acid. Apart from pharmaceutically acceptable acid addition salts, other salts are also included within the scope of acid addition salts such as, for example, those with picric or oxalic acids; they may serve as intermediates in the purification of the compounds or in the preparation of other, for example pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification of the bases. When the compounds of the invention contain an acid group, cationic salts can be prepared such as inorganic salts formed with alkali or alkaline earth metal metals especially sodium and potassium, or organic base salts such as ammonium or tetramethylammonium.

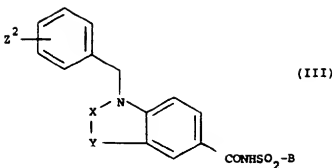
The invention also includes a process which comprises

(i) reacting a compound of the formula



in which A, X and Y have the values given them above and Z^1 is a leaving group, with a sulphonamide of the formula BSO_2NH_2 , or a salt thereof, to give a compound of formula (I), or

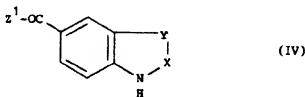
(ii) converting a compound of the formula



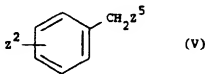
in which Z² is -NH₂ or -CO₂H, to a compound of formula (I) in which A is -NHCOR¹, -NHCOOR¹, -NHCONHR¹, -NHCSNHR¹ or -CONHR¹.

15 With regard to process (i), the reaction is preferably carried out at a temperature of from 0°C to 150°C and in the presence of an organic solvent, such as for example dichloromethane, toluene or tetrahydrofuran. Compounds of formula (II) bear a reactive -CO-Z¹ substituent, where Z¹ is a leaving group such as for example -OZ³ where Z³ is C₁₋₄ alkyl, or -OH combined with an activating agent such as dicyclohexyl carbodiimide, 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide, diphenyl carbamoyl chloride, or o-toluene sulphonyl isocyanate.

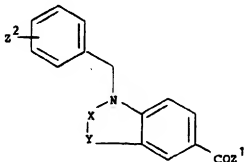
20 Formula (II) compounds can readily be prepared from known compounds by well known methods. Starting from a substituted fused ring compound of the formula



the basic cyclic system is synthesised by reaction with



40 where Z² is a group selected from -NO₂, -COZ⁴ or -CN, where Z⁴ is -OC₁₋₄ alkyl and Z⁵ is halo, to give the compound



The Z² group can be converted to one of the desired values of A by conventional means. For example, when Z² is -NO₂ reduction to amine then reaction with acyl halide gives compounds in which A is -NHCOR¹ and with

the chloroformate gives compounds in which A is -NHCOOR¹. Reaction of the amine with isocyanate or thiocyanate gives compounds in which A is -NHCONHR¹ and -NHCSNHR¹, respectively. Reaction of compounds in which Z² is -COZ⁴ with amine yields compounds in which A is -CONHR¹.

The 5-carbomethoxy indoles of formula (IV) above are known compounds as are others of this type, and can, for example, be made by the procedure of Leimgruber and Batcho, *Organic Synthesis Coll. Vol. V*, 214-224. The indolines of formula (IV) above can, for example, be synthesised from the corresponding indoles by catalytic hydrogenation.

The compounds of the invention are pharmacologically active, being leukotriene antagonists as shown by the test of Fleisch et al. (*J. Pharmacol. Exp. Ther.*, **233**, 148-157). Isolated guinea pig tracheal strip was suspended in Krebs solution at 37°C and aerated with 95% oxygen and 5% carbon dioxide. Concentration response curves to leukotriene (LTC₄ and LTD₄) were generated and the effects of different concentration of drug investigated. Dissociation constants (K_d) of the receptor-inhibitor complex were calculated by the method of Furchgott (Furchgott R.F. *Handbook of Experimental Pharmacology*, New York, Vol. 33 pages 383-385). The compounds of the invention disclosed in the following Examples had a pK_d of greater than 7. The compounds were also active in the total pulmonary resistance test (see Fleisch et al. above). Measurement of bronchospasm was recorded as an increase in tracheal resistance produced by LTD₄ administered intravenously into anaesthetised artificially ventilated guinea pigs. Also compounds of the invention are active in the *in vivo* Guinea Pig Pulmonary Function Test of Austen and Drazen (1974) *J. Clin. Invest.* **53**, 1679-1685 at intravenous dosage levels of from 0.05 µg to 5.0 mg/kg and in a modified "Herxheimer" test (*Journal of Physiology (London)* **117**, 251 (1952) at doses of from 25 to 200 mg/kg. The "Herxheimer" test is based on an LTD₄-induced bronchospasm in guinea pigs which closely resembles an asthmatic attack in man.

The compounds are accordingly indicated for therapeutic use in the treatment of diseases in which leukotrienes are implicated. These include allergic reactions of the pulmonary system in which leukotrienes are thought to be causal mediators of bronchospasm, for example, in allergic lung disorders such as extrinsic asthma and industrial asthmas such as Farmers lung, and in other inflammatory disorders, for example, associated with acute or chronic infectious diseases such as allergic skin diseases, eczopic and atopic eczemas, psoriasis, contact hypersensitivity and angioneurotic oedema, bronchitis and cystic fibrosis and rheumatic fever.

The compounds of the invention also have potential in the treatment of vascular diseases such as shock and ischaemic heart diseases for example coronary artery disease and myocardial infarction, cerebrovascular diseases, and renal diseases for example renal ischaemia.

Thus the invention also includes a pharmaceutical composition comprising a pharmaceutically acceptable diluent or carrier in association with a compound of formula (I) in unprotected form; or a pharmaceutically acceptable salt thereof.

The compounds may be administered by various routes, for example by the oral or rectal route, topically or parenterally, for example by injection or infusion, and especially by inhalation, being usually employed in the form of a pharmaceutical composition. Such compositions are prepared in a manner well known in the pharmaceutical art and normally comprise at least one active compound. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders. The compounds of the invention are particularly suitable for administration by inhalation, in forms of presentation which include, for example, aerosols, atomisers and vaporisers.

Some examples of suitable carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl- hydroxybenzoate, talc magnesium stearate and mineral oil. The compositions of the injection may, as is well known in the art, be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient.

Where the compositions are formulated in unit dosage form, it is preferred that each unit dosage form contains from 5 mg to 500 mg, for example, from 25 mg to 200 mg. The term "unit dosage form" refers to physically discrete units suitable as unit dosages for human subjects and animals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier.

The active compounds are effective over a wide dosage range and, for example, dosages per day will normally fall within the range of from 0.5 to 300 mg/kg, more usually in the range of from 5 to 100 mg/kg. However,

it will be understood that the amount administered will be determined by the physician in the light of the relevant circumstances including the condition to be treated, the choice of compound to be administered and the chosen route of administration, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way.

The invention is illustrated by the following Examples.

EXAMPLE 1

Methyl 1-(3-nitrobenzyl)indole-5-carboxylate

Methyl indole-5-carboxylate (10 g) was dissolved in dry tetrahydrofuran (250 ml) and cooled in an ice-bath. To the stirred solution was added sodium hydride (60% suspension in oil) (2.57 g) in portions over 15 minutes. After stirring for a further 30 minutes, 3-nitrobenzyl bromide (11.55 g) in dry tetrahydrofuran (30 ml) was added dropwise over 20 minutes. Stirring was continued at 0°C for 30 minutes, then at room temperature for 2 hours. Excess sodium hydride was destroyed by cautious addition of acetic acid, then the reaction mixture extracted from brine into ethyl acetate, dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. Recrystallisation from ethyl acetate/hexane afforded methyl 1-(3-nitrobenzyl)indole-5-carboxylate (m.p. 129-130°C).

EXAMPLE 2

1-(3-Nitrobenzyl)indole-5-carboxylic acid

To a solution of the methyl ester (Example 1) (12.5 g) in tetrahydrofuran (150 ml) and methanol (300 ml) was added 2N sodium hydroxide (78 ml). The reaction mixture was heated under reflux for 4 hours, then cooled. The volume was reduced *in vacuo* to approximately 100 ml. and the solution acidified with 5N hydrochloric acid. On cooling, the crystalline product was filtered off and dried *in vacuo* in the oven at 50°C to give 1-(3-nitrobenzyl)indole-5-carboxylic acid (m.p. 251-254°C).

EXAMPLE 3

N-[1-(3-nitrobenzyl)indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

The carboxylic acid (Example 2) (6.2 g) was stirred at room temperature in dichloromethane (50 ml) with 2-methylbenzene sulphonamide (3.4 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.6 g) and 4-dimethylaminopyridine (0.25 g) for 72 hours. The reaction mixture was diluted with dichloromethane and washed with 0.5N hydrochloric acid, then water. The organic extract was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with 0-2% ethyl acetate in dichloromethane, afforded N-[1-(3-nitrobenzyl)indol-5-ylcarbonyl]-2-methylbenzene sulphonamide (m.p. 208-210°C).

EXAMPLE 4

N-[1-(3-aminobenzyl)indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

The nitrobenzylindole (Example 3) (2.7 g) was dissolved in methanol (125 ml) and ethyl acetate (125 ml), and 10% palladium on charcoal (0.5 g) added. The reaction mixture was hydrogenated in a Parr bottle at 50 p.s.i. with shaking until hydrogen uptake was complete (approximately 1 hour). The catalyst was filtered off through Celite and the solvent removed *in vacuo* to give N-[1-(3-aminobenzyl)indol-5-ylcarbonyl]-2-methylbenzene sulphonamide as a foam. This crude product was used in the next step without purification.

EXAMPLE 5

N-[1-(3-(n-Butoxycarbonylamino)benzyl)indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

The amine (Example 4) (0.17 g) was dissolved in dichloromethane (5 ml) and 2,6-lutidine (50 µl) and stirred as n-butyl chloroformate (55 µl) was added over 2 minutes. The reaction mixture was stirred for 3 hours, diluted with dichloromethane and washed with 0.5N hydrochloric acid, then water. The organic extract was dried over

anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with 0-5% ethyl acetate in dichloromethane, yielded N-{1-[3-(*n*-butoxycarbonylamino)benzyl]indol-5-ylcarbonyl}-2-methylbenzene sulphonamide as a gum.

- 5 ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.89 (3H,t), 1.33 (2H,m), 1.56 (2H,m), 2.62 (3H,s), 4.02 (2H,t), 5.42 (2H,s), 6.66 (1H,d), 6.78 (1H,m), 7.19 (1H,t), 7.32 (1H,m), 7.35 (1H,m), 7.39 (1H,m), 7.46 (1H,m), 7.50 (1H,d), 7.58 (1H,m), 7.60 (1H,d), 7.63 (1H,dd), 8.05 (1H,dd), 8.28 (1H,d), 9.58 (1H,s), 12.4 (1H, bs).

EXAMPLES 6-16

- 10 Using a similar procedure to that described in Example 5, the amine (Example 4) was reacted with the appropriate chloroformate to give the following compounds:

EXAMPLE 6

- 15 N-{1-[3-(*n*-butoxycarbonylamino)benzyl]indol-5-ylcarbonyl}-2-methylbenzene sulphonamide, m.p. 179-181°C. ¹H NMR (DMSO-*d*₆, 300 MHz) δ 0.89 (6H,d), 1.86 (1H,m), 2.62 (3H,s), 3.81 (2H,d), 5.42 (2H,s), 6.65 (1H,d), 6.77 (1H,dd), 7.18 (1H,m), 7.31 (2H,m), 7.39 (1H,m), 7.43 (1H,m), 7.47 (1H,m), 7.55 (1H,m), 7.58 (1H,d), 7.62 (1H,dd), 8.03 (1H,dd), 8.26 (1H,d), 9.59 (1H,s).

EXAMPLE 7

N-{1-[3-(Benzyloxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 25 ¹H NMR (DMSO-*d*₆, 300 MHz) δ 2.62 (3H,s), 5.10 (2H,s), 5.42 (2H,s), 6.65 (1H,d), 6.78 (1H,m), 7.20 (1H,t), 7.32 (1H,m), 7.3-7.4 (7H), 7.45 (1H,m), 7.48 (1H,m), 7.54 (1H,m), 7.58 (1H,d), 7.64 (1H,dd), 8.03 (1H,dd), 8.26 (1H,d), 9.75 (1H,s).

EXAMPLE 8

N-{1-[3-(Cyclopentylmethoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 30 ¹H NMR (CDCl₃, 300 MHz) δ 1.5-1.8 (8H), 2.20 (1H,m), 2.75 (3H,s), 4.05 (2H,d), 5.30 (2H,s), 6.58 (1H,s), 6.65 (1H,d), 6.75 (1H,d), 7.2-7.6 (9H), 8.10 (1H,d), 8.30 (1H,dd), 8.85 (1H,bs).

EXAMPLE 9

N-{1-[3-(Cyclobutylmethoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 40 ¹H NMR (CDCl₃, 300 MHz) δ 1.75-2.10 (6H,m), 2.65 (1H,m), 2.70 (3H,s), 4.10 (2H,d), 5.30 (2H,s), 6.55 (1H,s), 6.65 (1H,d), 6.70 (1H,m), 7.15-7.6 (9H), 8.10 (1H,d), 8.30 (1H,dd), 8.65 (1H,bs).

EXAMPLE 10

N-{1-[3-(Cyclopropylmethoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 45 ¹H NMR (CDCl₃, 300 MHz) δ 0.30 (2H,m), 0.58 (2H,m), 1.13 (1H,m), 2.72 (3H,s), 3.96 (2H,d), 5.31 (2H,s), 6.57 (1H,s), 6.64 (1H,d), 6.74 (1H,m), 7.1-7.3 (6H), 7.41 (1H,m), 7.51 (1H,m), 7.59 (1H,m), 8.11 (1H,d), 8.28 (1H,dd), 8.71 (1H,bs).

EXAMPLE 11

N-{1-[3-(2-methylbutoxycarbonylamino)benzyl]indol-5-ylcarbonyl}-2-methylbenzene sulphonamide

- 55 ¹H NMR (CDCl₃, 300 MHz) δ 0.91 (3H), 0.92 (3H), 1.2-1.6 (2H,m), 1.70 (1H,m), 2.72 (3H,s), 3.9-4.1 (2H,m), 5.31 (2H,s), 6.54 (1H,s), 6.64 (1H,d), 6.72 (1H,d), 7.2-7.4 (6H), 7.42 (1H,m), 7.52 (1H,m), 7.58 (1H,dd), 8.10 (1H,d), 8.29 (1H,dd), 8.68 (1H,bs).

EXAMPLE 12N-{1-[3-(2-methylbut-3-enyloxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 5 ¹H NMR (CDCl₃, 300 MHz) δ 1.04 (3H,d), 2.55 (1H,m), 2.70 (3H,s), 4.00 (2H,m), 5.05 (2H,m), 5.30 (2H,s), 5.75 (1H,m), 6.55 (1H,s), 6.65 (1H,d), 6.75 (1H,m), 7.15-7.3 (6H), 7.42 (1H,m), 7.50 (1H,m), 7.58 (1H,dd), 8.10 (1H,d), 8.30 (1H,dd), 8.75 (1H,bs).

EXAMPLE 13N-{1-[3-(Isopropoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 10 ¹H NMR (CDCl₃, 300 MHz) δ 1.25 (6H,d), 2.70 (3H,s), 4.98 (1H,m), 5.30 (2H,s), 6.45 (1H,bs), 6.65 (1H,d), 6.75 (1H,m), 7.15-7.35 (6H), 7.41 (1H,m), 7.51 (1H,m), 7.56 (1H,dd), 8.10 (1H,d), 8.28 (1H,dd), 8.60 (1H,s).

EXAMPLE 14N-{1-[3-(Propoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 20 ¹H NMR (CDCl₃, 300 MHz) δ 0.95 (3H,t), 1.66 (2H,m), 2.72 (3H,s), 4.09 (2H,t), 5.30 (2H,s), 6.53 (1H,d), 6.64 (1H,d), 6.74 (1H,m), 7.2-7.4 (6H), 7.40 (1H,m), 7.49 (1H,m), 7.57 (1H,dd), 8.11 (1H,s), 8.31 (1H,d), 8.65 (1H,bs).

EXAMPLE 15N-{1-[3-(1-Methylpropoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 25 ¹H NMR (CDCl₃, 300 MHz) δ 0.92 (3H,t), 1.24 (3H,d), 1.58 (2H,m), 2.72 (3H,s), 4.81 (1H,m), 5.31 (2H,s), 6.49 (1H,s), 6.65 (1H,m), 6.72 (1H,m), 7.2-7.3 (6H), 7.42 (1H,t), 7.51 (1H,m), 7.58 (1H,m), 8.11 (1H,d), 8.29 (1H,dd), 8.62 (1H,s).

EXAMPLE 16N-{1-[3-(2-Methyl-2-propenyloxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 35 ¹H NMR (CDCl₃, 300 MHz) δ 1.77 (3H,s), 2.72 (3H,s), 3.5 (1H,b), 4.56 (2H,s), 4.94 (1H,bs), 4.99 (1H,bs), 5.31 (2H,s), 6.60 (1H,bs), 6.65 (1H,d), 6.74 (1H,dd), 7.2-7.6 (8H,m), 8.10 (1H,d), 8.29 (1H,d), 8.61 (1H,s).

EXAMPLE 17N-{1-[3-(1-Methyl-2,2,2-trifluoroethoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 40 ¹H NMR (CDCl₃, 300 MHz) δ 1.45 (3H,d), 2.72 (3H,s), 3.5 (1H,b), 5.30 (1H,m), 5.34 (2H,s), 6.68 (2H,m), 6.80 (1H,m), 7.18 (1H,m), 7.2-7.35 (4H), 7.42 (1H,m), 7.50 (1H,m), 7.60 (1H,dd), 8.12 (1H,d), 8.30 (1H,dd), 8.65 (1H,bs).

EXAMPLE 18N-{1-[3-(2-Methyl-1,3,3,3-trifluoropropoxycarbonylamino)benzyl]indol-5-yl-carbonyl}-2-methylbenzene sulphonamide

- 50 ¹H NMR (CDCl₃, 300 MHz) δ 1.70 (3H,d), 2.58 (1H,m), 2.71 (3H,s), 4.17 (1H,dd), 4.38 (1H,dd), 5.30 (2H,s), 6.63 (1H,s), 6.65 (1H,dd), 6.75 (1H,d), 7.10-7.35 (6H,m), 7.42 (1H,t), 7.50 (1H,dt), 7.58 (1H,dd), 8.12 (1H,d), 8.28 (1H,dd), 8.8 (1H,b).

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EXAMPLE 19

N-[1-[3-(2,2,3,3,3-Pentafluoropropoxycarbonylamino)benzyl]-indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

¹H NMR (CDCl₃, 300 MHz) δ 2.72 (3H,s), 4.60 (2H,t), 5.30 (2H,s), 6.64 (1H,d), 6.80 (2H,m), 7.15 (1H,s), 7.21 (1H,d), 7.25-7.30 (4H,m), 7.40 (1H,t), 7.51 (1H,dt), 7.60 (1H,dd), 8.13 (1H,d), 8.29 (1H,dd).

EXAMPLE 20

Methyl 1-[3-(cyclopentylloxycarbonylamino)benzyl]-indole-5-carboxylate

The nitrobenzylindole (Example 1) (0.64 g) was dissolved in methanol (50 ml) and 10% palladium on charcoal (0.1 g) added. The reaction mixture was hydrogenated in a Parr bottle at 50 p.s.i. with shaking until hydrogen uptake was complete (approximately 1 hour). The catalyst was filtered off through Celite and the solvent removed in vacuo.

The crude amine was dissolved in dichloromethane (15 ml) and 2,6-lutidine (0.22 g), and cooled in an ice-bath. Cyclopentyl chloroformate (0.31 g) in dichloromethane (1 ml) was added dropwise to the stirred solution over 2 minutes. After stirring for 10 minutes at 0°C, the ice-bath was removed and the reaction mixture stirred for a further 2 hours at room temperature. The solvent was removed in vacuo and the crude product purified by flash chromatography on silica, eluting with 25% ethyl acetate in hexane, to give methyl 1-[3-(cyclopentylloxycarbonylamino)benzyl]-indole-5-carboxylate, m.p. 131-133°C.

EXAMPLE 21

N-[1-[3-(Cyclopentylloxycarbonylamino)benzyl]-indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

To a solution of the methyl ester (Example 20) (0.7 g) in tetrahydrofuran (8 ml) and methanol (4 ml) was added 2N lithium hydroxide (1.7 ml), and the reaction mixture heated under reflux for 3 hours. The cooled solution was acidified with 2N hydrochloric acid and the product extracted into chloroform. The organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo.

The crude carboxylic acid was stirred at room temperature in dichloromethane (7 ml) with 2-methylbenzene sulphonamide (0.27 g), 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (0.37 g) and 4-dimethylaminopyridine (0.1 g) for 48 hours. The reaction mixture was diluted with dichloromethane and washed with 0.5N hydrochloric acid, then water. The organic extract was dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. Purification by flash chromatography on silica, eluting with 50-80% diethyl ether in 40-60°C petroleum ether, followed by crystallisation from dichloromethane/60-80°C petroleum ether afforded N-[1-[3-(cyclopentylloxycarbonylamino)benzyl]-indol-5-ylcarbonyl]-2-methylbenzene sulphonamide, m.p. 188-190°C.

¹H NMR (CDCl₃, 300 MHz) δ 1.69 (8H,m), 2.72 (3H,s), 5.15 (1H,s), 5.28 (2H,s), 6.60 (2H,m), 6.70 (1H,m), 7.1-7.4 (6H), 7.43 (1H,t), 7.51 (1H,m), 7.60 (1H,m), 8.13 (1H,s), 8.30 (1H,d), 9.00 (1H,s).

EXAMPLE 22

N-[1-[3-(3-Methylbutylcarbonylamino)benzyl]indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

A mixture of the amine (Example 4) (0.25 g), 3-methyl-valeric acid (0.07 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.126 g) and 4-dimethylaminopyridine (0.02 g) in dichloromethane (5 ml) was stirred at room temperature for 96 hours. The reaction mixture was washed with water then saturated brine, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. Purification by flash chromatography on silica, eluting with 0-30% ethyl acetate in hexane, afforded N-[1-[3-(3-methylbutylcarbonylamino)benzyl]indol-5-ylcarbonyl]-2-methylbenzene sulphonamide.

¹H NMR (CDCl₃, 300 MHz) δ 0.91 (6H,d), 1.58 (1H,m), 1.55 (2H,m), 2.30 (2H,m), 2.71 (3H,s), 5.31 (2H,s), 6.63 (1H,d), 6.78 (1H,d), 7.09 (1H,s), 7.2-7.4 (6H), 7.41 (1H,t), 7.51 (1H,m), 7.56 (1H,m), 8.09 (1H,d), 8.28 (1H,dd), 8.73 (1H,s).

EXAMPLE 23N-[1-[3-(Butylcarbonylamino)benzyl]indol-5-ylcarbonyl]-2-methyl benzene sulphonamide

- 5 Using a similar procedure to that described in Example 22, the amine (Example 4) was reacted with butyric acid to give N-[1-[3-(butylcarbonylamino)benzyl]indol-5-ylcarbonyl]-2-methyl-benzene sulphonamide.
 'H NMR (CDCl₃, 300 MHz) δ 0.90 (3H,t), 1.35 (2H,m), 1.63 (2H,m), 2.28 (2H,t), 2.70 (3H,s), 5.27 (2H,s), 6.60 (1H,d), 6.77 (1H,d), 7.1-7.6 (10H), 8.08 (1H,s), 8.27 (1H,d), 8.9 (1H,bs).

10 EXAMPLE 24N-[1-[3-(3-Methyl-1-butenylcarbonylamino)benzyl]indol-5-yl-carbonyl]-2-methylbenzene sulphonamide

- 15 Using a similar procedure to that described in Example 22, the amine (Example 4) was reacted with 3-methyl-1-butenic acid to give N-[1-[3-(3-methyl-1-butenylcarbonylamino)-benzyl]indol-5-yl carbonyl]-2-methyl-benzene sulphonamide.
 'H NMR (CHCl₃, 300 MHz) δ 1.00 (3H,s), 1.03 (3H,s), 2.45 (1H,m), 2.62 (3H,s), 5.45 (2H,s), 6.00 (1H,dd), 6.66 (1H,d), 6.77 (1H,dd), 6.87 (1H,d), 7.23 (1H,t), 7.4-7.6 (8H,m), 8.20 (1H,d), 8.27 (1H,dd), 9.92 (1H,s).

20 EXAMPLE 25N-[1-[3-(3-Propyl-1-ureido)benzyl]indol-5-ylcarbonyl]-2-methyl-benzene sulphonamide

- A mixture of the amine (Example 4) (0.25 g) and n-propyl isocyanate (0.051 g) in dichloromethane (5 ml) was stirred at room temperature for 24 hours. The reaction mixture was washed with water then saturated brine, dried over magnesium sulphate, filtered and evaporated *in vacuo*. Purification by flash chromatography on silica (eluant 0-100% ethyl acetate in hexane), followed by preparative reverse phase HPLC (1 inch LP1-ODS column; 60:40:0.1 methanol:water:acetic acid) gave N-[1-[3-(3-propyl-1-ureido)benzyl]indol-5-ylcarbonyl]-2-methylbenzene sulphonamide.
 30 'H NMR (CDCl₃, 300 MHz) δ 0.82 (3H,t), 1.41 (2H,m), 2.72 (3H,s), 3.03 (2H,m), 3.49 (1H,s), 4.8 (1H,bs), 5.22 (2H,s), 6.50 (2H,m), 6.75 (1H,m), 7.0-7.3 (5H), 7.3-7.5 (3H), 8.03 (1H,d), 8.27 (1H,dd), 9.3 (1H,bs).

EXAMPLE 2635 N-[1-[3-(3-Isobutyl-1-thioureido)benzyl]indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

- A mixture of the amine (Example 4) (0.35 g) and isobutyl isothiocyanate (0.116 g) in dichloromethane (5 ml) was stirred at room temperature for 72 hours, then heated under reflux for 4 hours. The reaction mixture was washed with water then saturated brine, dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. Purification by flash chromatography on silica (eluant 20-40% ethyl acetate in hexane), followed by preparative reverse-phase HPLC (1 inch LP1-ODS column; 60:40:0.1 methanol:water:acetic acid), gave N-[1-[3-(3-isobutyl-1-thioureido)benzyl]indol-5-ylcarbonyl]-2-methylbenzene sulphonamide.
 40 'H NMR (CDCl₃, 300 MHz) δ 0.88 (6H,d), 1.75 (1H,m), 2.70 (3H,s), 3.30 (2H,t), 5.35 (2H,s), 5.9 (1H,bs), 6.65 (1H,d), 6.75 (1H,d), 7.0-7.6 (8H), 7.62 (1H,dd), 8.10 (1H,d), 8.30 (1H,dd).

45 EXAMPLE 27N-[1-[3-(3-Propyl-1-thioureido)benzyl]indol-5-ylcarbonyl]-2-methylbenzene sulphonamide

- 50 Using a similar procedure to that described in Example 26, the amine (Example 4) was reacted with propyl isothiocyanate to give N-[1-[3-(3-propyl-1-thioureido)benzyl]-[indol-5-ylcarbonyl]-2-methylbenzene sulphonamide.
 'H NMR (CDCl₃, 300 MHz) δ 0.89 (3H,t), 1.43 (2H,m), 2.71 (3H,s), 3.45 (2H,q), 5.36 (2H,s), 5.84 (1H,bs), 6.68 (1H,d), 6.74 (1H,s), 7.05 (1H,dd), 7.12 (1H,dd), 7.24 (1H,d), 7.3-7.5 (4H), 7.5-7.6 (2H), 7.61 (1H,dd), 8.12 (1H,d), 8.30 (1H,dd).

EXAMPLE 281-[3-(isobutoxycarbonylamino)benzyl]indole-5-carboxylic acid

5 The nitrobenzylindole (Example 2) (3 g) was dissolved in methanol (100 ml) and tetrahydrofuran (100 ml), and 10% palladium on charcoal (0.25 g) added. The reaction mixture was hydrogenated in a Parr bottle at 60 p.s.i. with shaking until hydrogen uptake was complete. The catalyst was filtered off through Celite and the solvent removed in vacuo.

10 The crude amine was dissolved in tetrahydrofuran (100 ml) and sodium bicarbonate (1.63 g) in water (15 ml) added. The reaction mixture was stirred as isobutyl chloroformate (1.59 g) was added dropwise over 5 minutes. Stirring was continued for 2 hours, then the reaction was acidified with acetic acid and extracted from saturated brine into ethyl acetate. The organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. Recrystallisation from ethyl acetate/hexane afforded 1-[3-(isobutoxycarbonylamino)benzyl]-indole-5-carboxylic acid, m.p. 173-176°C.

EXAMPLE 29N-{1-[3-(isobutoxycarbonylamino)benzyl]indol-5-ylcarbonyl}-benzene sulphonamide

20 The carboxylic acid (Example 28) (0.25 g) was stirred at room temperature in dichloromethane (3 ml) with benzene sulphonamide (0.10 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.15 g) and 4-dimethylaminopyridine (0.02 g) for 144 hours. The reaction mixture was diluted with chloroform and washed with 0.5N hydrochloric acid, then water. The organic extract was dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. Purification by preparative reverse-phase HPLC (1 inch LP1-ODS column), eluting with 75:25: 0.1 methanol:water:acetic acid, gave N-{1-[3-(isobutoxycarbonylamino)benzyl]indol-5-ylcarbonyl}benzene sulphonamide.

25 ¹H NMR (DMSO, 300 MHz) δ 0.89 (6H,d), 1.87 (1H,m), 3.82 (2H,d), 5.41 (2H,s), 6.63 (1H,d), 6.77 (1H,d), 7.19 (1H,t), 7.32 (2H,m), 7.45 (1H,d), 7.5-7.7 (6H), 7.98 (2H,m), 8.22 (1H,d), 9.60 (1H,s).

EXAMPLE 30N-{1-[3-(isobutoxycarbonylamino)benzyl]indol-5-ylcarbonyl}-2-chlorobenzene sulphonamide

35 Using a similar procedure to that described in Example 29, the carboxylic acid (Example 28) was reacted with 2-chlorobenzene sulphonamide to give N-{1-[3-(isobutoxycarbonylamino)benzyl]indol-5-ylcarbonyl}-2-chlorobenzene sulphonamide.

¹H NMR (DMSO-d₆, 300 MHz) δ 0.90 (6H,d), 1.85 (1H,m), 3.82 (2H,d), 5.42 (2H,s), 6.65 (1H,d), 6.78 (1H,d), 7.18 (1H,m), 7.30 (2H,m), 7.50 (1H,d), 7.58 (1H,d), 7.6-7.75 (5H), 8.18 (1H,d), 8.30 (1H,d), 9.65 (1H,s).

EXAMPLE 31Methyl indoline-5-carboxylate

45 Methyl indole-5-carboxylate (5 g) was dissolved in methanol (300 ml) containing concentrated sulphuric acid (12 ml) and 10% palladium on charcoal (1.0 g) added. The reaction mixture was hydrogenated in a Parr bottle at 65 p.s.i. with shaking for 48 hours. The catalyst was filtered off through Celite. The solution was made basic by addition of ammonia solution (0.880) and evaporated in vacuo. The product was extracted from water into ethyl acetate, the organic extracts dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo to give methyl indoline-5-carboxylate, m.p. 70-72°C.

EXAMPLE 32Methyl 1-(3-nitrobenzyl)indoline-5-carboxylate

55 A mixture of the indoline (Example 31) (4.39 g), 3-nitrobenzyl bromide (5.02 g) and anhydrous potassium carbonate (3.17 g) in methyl ethyl ketone (150 ml) was heated under reflux for 18 hours. On cooling, the inorganics were filtered off and the solvent removed in vacuo. The reaction mixture was extracted from water into ethyl acetate, dried over anhydrous magnesium sulphate, filtered and evaporated in vacuo. Purification by flash

chromatography on silica, eluting with chloroform, gave methyl 1-(3-nitrobenzyl)indoline-5-carboxylate, m.p. 99-100°C.

EXAMPLE 33

1-(3-Nitrobenzyl)indoline-5-carboxylic acid

A suspension of the methyl ester (Example 32) (5.72 g) in 2N sodium hydroxide (35 ml) and methanol (140 ml) was heated under reflux for 6 hours. The reaction mixture was cooled and concentrated *in vacuo*. Acidification with aqueous hydrochloric acid and filtration gave 1-(3-nitrobenzyl)indoline-5-carboxylic acid, m.p. 259-262°C.

EXAMPLE 34

N-[1-(3-Nitrobenzyl)indolin-5-ylcarbonyl]-2-methylbenzene sulphonamide

A mixture of the carboxylic acid (Example 33) (0.5 g), 2-methylbenzene sulphonamide (0.28 g), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.37 g) and 4-dimethylaminopyridine (0.05 g) in dichloromethane (6 ml) was stirred at room temperature for 72 hours. The reaction mixture was diluted with dichloromethane and washed with water and brine. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. Purification by flash chromatography on silica, eluting with 0-2% ethyl acetate in dichloromethane, gave a yellow oil which, on crystallisation from methanol, afforded N-[1-(3-nitrobenzyl)indolin-5-ylcarbonyl]-2-methylbenzene sulphonamide, m.p. 159-163°C.

EXAMPLE 35

N-[1-(3-(Isobutoxycarbonylamino)benzyl)indolin-5-ylcarbonyl]-2-methylbenzene sulphonamide

The nitrobenzylindoline (Example 34) (0.35 g) was dissolved in ethyl acetate (50 ml) and 10% palladium on charcoal (0.1 g) added. The reaction mixture was hydrogenated in a Parr bottle at 50 p.s.i. with shaking until hydrogen uptake was complete. The catalyst was filtered off through Celite and the solvent removed *in vacuo*.

The crude amine was dissolved in dichloromethane (15 ml) and 2,6-lutidine (90 µl), and cooled in an ice-bath. Isobutyl chloroformate (0.11 g) in dichloromethane (5 ml) was added dropwise to the stirred solution over 5 minutes. The ice-bath was removed and the reaction mixture stirred for a further 3.5 hours at room temperature. The solution was washed with aqueous hydrochloric acid, water and saturated brine. The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. An initial purification was carried out by flash chromatography on silica, eluting with 2.5-7.5% ethyl acetate in dichloromethane. Further purification by preparative reverse-phase HPLC (1 inch LP1-ODS column), eluting with methanol:water:acetic acid (70:30:0.1), gave N-[1-(3-(isobutoxycarbonylamino)benzyl)indolin-5-ylcarbonyl]-2-methylbenzene sulphonamide.

¹H NMR (CDCl₃, 300 MHz) δ 0.95 (6H,d), 1.96 (1H,m), 2.69 (3H,s), 3.02 (2H,t), 3.54 (2H,t), 3.93 (2H,d), 4.34 (2H,s), 6.35 (1H,d), 6.66 (1H,s), 6.94 (1H,m), 7.25-7.45 (4H), 7.45-7.55 (3H), 8.25 (1H,dd), 8.7 (1H,bs).

The following formulations illustrate the invention.

EXAMPLE 36

Soft gelatin capsule

Each soft gelatin capsule contains:

Active ingredient	150 mg
Arachis oil	150 mg

After mixing together, the blend is filled into soft gelatin capsules using the appropriate equipment.

EXAMPLE 37**Hard gelatin capsule**

5 Each capsule contains:

Active ingredient 50 mg

PEG 4000 250 mg

The PEG 4000 is melted and mixed with the active ingredient. Whilst still molten the mixture is filled into capsule shells and allowed to cool.

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EXAMPLE 38**Aerosol**

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Active ingredient	10 mg
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Ethanol	50 mg
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Dichlorodifluoromethane (Propellant 12)	658 mg
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Dichlorotetrafluoroethane (Propellant 14)	282 mg
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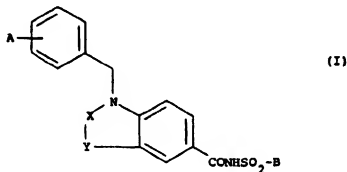
The active ingredient is dissolved in the ethanol. The concentrate is filled into extruded aluminium cans for inhalation aerosols. The cans are degassed with propellant 12 and sealed with an appropriate metered dose valve. The volume of product expelled per actuation is 50 to 100 μ l equivalent to 0.5-1 mg active ingredient.

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Claims

1. A compound of the formula

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in which A is selected from -NHCOR¹, -NHCOOR¹, -NHCONHR¹, -NHCSNHR¹, -CONHR¹, where R¹ is optionally halo-substituted C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₃₋₇ cycloalkyl-C₁₋₄ alkyl or phenyl-C₁₋₄ alkyl, B is optionally substituted phenyl, and -X-Y- is -CH=CH- or -CH₂CH₂-; and salts thereof.

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2. A compound according to claim 1, in which A is -NHCOR¹, -NHCOOR¹, -NHCSNHR¹ or -NHCONHR¹.

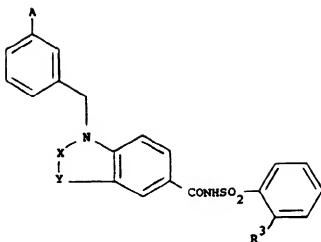
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3. A compound according to either of claims 1 and 2, in which R¹ is benzyl, C₁₋₄ alkyl or halo-substituted C₁₋₄ alkyl.

4. A compound according to any of the preceding claims, in which B is a phenyl ring substituted with a single substituent selector from C₁₋₄ alkyl, C₁₋₄ alkoxy and halogen.

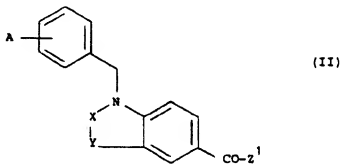
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5. A compound of the formula

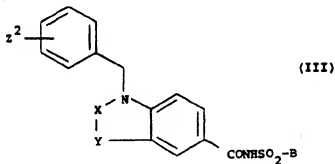


in which A is -NHCOR¹, -NHCOOR¹, -NHCSNHR¹ or -NHCONHR¹, -X-Y- is -CH=CH- or -CH₂-CH₂-, R¹ is benzyl, C₁₋₄ alkyl or halo-substituted C₁₋₄ alkyl and R³ is C₁₋₄ alkyl, C₁₋₄ alkoxy or halogen.

6. A process for providing a compound according to claim 1, which comprises
(i) reacting a compound of the formula



in which A, X and Y have the values given them above and Z' is a leaving group, with a sulphonamide of the formula BSO₂NH₂, or a salt thereof, to give a compound of formula (I), or
(ii) converting a compound of the formula



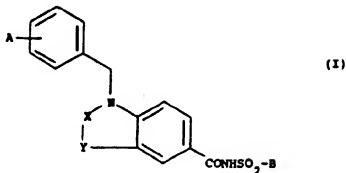
in which Z² is -NH₂ or -CO₂H, to a compound of formula (I) in which A is -NHCOR¹, -NHCOOR¹, -NHCONHR¹, -NHCSNHR¹ or -CONHR¹.

7. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, for use as a pharmaceutical.
8. A pharmaceutical formulation comprising a compound according to claim 1, or a pharmaceutically-acceptable

able salt thereof, together with a diluent or carrier therefor.

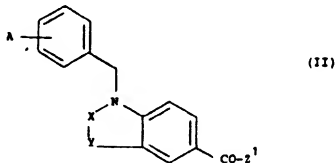
Claims for the following Contracting States: ES, GR

1. A process for producing a compound of the formula



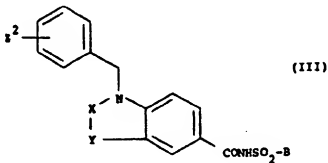
in which A is selected from -NHCOR^1 , -NHCOOR^1 , -NHCONHR^1 , -NHCSNHR^1 , -CONHR^1 , where R^1 is optionally halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{3-7} cycloalkyl- C_{1-4} alkyl or phenyl- C_{1-4} alkyl, B is optionally substituted phenyl, and -X-Y- is -CH=CH- or $\text{-CH}_2\text{-CH}_2\text{-}$; or a salt thereof; which comprises

(i) reacting a compound of the formula



in which A, X and Y have the values given them above and Z^1 is a leaving group, with a sulphonamide of the formula BSO_2NH_2 , or a salt thereof, to give a compound of formula (I) or

(ii) converting a compound of the formula



in which Z^2 is -NH_2 or $\text{-CO}_2\text{H}$, to a compound of formula (I) in which A is NHCOR^1 , -NHCOOR^1 , -NHCONHR^1 , -NHCSNHR^1 or -CONHR^1 .

2. A process according to claim 1, for producing a compound in which A is -NHCOR^1 , -NHCOOR^1 , -NHCSNHR^1 OR -NHCONHR^1 .

3. A process according to either of claims 1 and 2, for producing a compound in which R¹ is benzyl, C₁₋₄ alkyl or halo-substituted C₁₋₄ alkyl.
4. A process according to any of the preceding claims for producing a compound in which B is a phenyl ring substituted with a single substituent selector from C₁₋₄ alkyl, C₁₋₄ alkoxy and halogen.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 91308365.5
Category	Citation of document with indications, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	<u>EP - A - 0 242 167</u> (ICI AM.) * Claims 1,9,11 * ---	1, 2, 6, 8	C 07 D 209/08 A 61 K 31/40
A	<u>EP - A - 0 159 376</u> (HOECHST-ROUSSEL) * Claims 1.9 * ----	1, 8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			C 07 D 209/00
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
VIENNA	28-11-1991	HOCHHAUSER	
CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : documents cited for other reasons A : technological background O : non-written disclosure P : intermediate document	
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category		A : member of the same patent family, corresponding document	

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